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Clinically Relevant Adipose Tissue Engineering Strategies and Market Potential

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Clinically Relevant Adipose Tissue Engineering Strategies and Market Potential

by

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Thesis

Presented to the Faculty of the Graduate School
The University of Texas at Austin
in Partial Fulfillment
of the Requirements
for the Degree of

Master of Science in Engineering

The University of Texas at Austin
December 2010

Acknowledgements

I would like to thank:

Larry D. Swain, DDS, my mentor, for thoughtful discussions, reviewing and editing, as well as his encouragement throughout the duration of my graduate studies.

Neal K. Vail, PhD, my reader and mentor, for his input and review of this document, and his encouragement throughout the duration of my graduate studies.

Anthony P. Ambler, PhD, my advisor, for input on direction on the scope and content of this project.

My friends, family, and colleagues for support and encouragement.

Clinically Relevant Adipose Tissue Engineering Strategies and Market Potential

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The University of Texas at Austin, 2010
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This thesis presents a foundation for developing a business case for companies interested in the reconstructive and cosmetic procedure markets. The focus is on reviewing adipose tissue engineering research and proposing technology opportunities that could be applied to challenging soft tissue reconstruction cases and adjacently applied to cosmetic applications. To establish the foundation for this type of program, this thesis includes an evaluation of the reconstructive and cosmetic procedure markets, current practices in these markets and their constraints, as well as a literature review of research in adipose tissue engineering and its potential clinical applications. Additionally it captures the competitive landscape of major players in the reconstructive market as well as up-and-coming players in the adipose tissue engineering field. Technology development opportunities with associated customer and business value are discussed with a recommendation for the development of a detailed business case to evaluate specific product development opportunities in these markets.

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INTRODUCTION

Reconstructive surgery is a $1 billion market fraught with unmet needs due to large numbers of people in the world presenting a vast array of clinical challenges. This market includes patients with a wide-range of medical issues including a great deal of variance in affliction sites, causes and severity of injuries, age of patients, and many other complications. The commonality in the market is generally the affliction to body contour and deficits in soft tissue, therefore treatment options and products available for reconstruction are often those developed for the cosmetic surgery market, estimated at $30 billion annually. Reconstructive treatment options should be adaptable to the varied circumstances and intervention requirements. However, for most patients this is not the case.

Though available market analyses focus on current treatment options, their growth potential, and advice for new entrants into the market, they do not provide a thorough evaluation of true market, patient-driven needs. This requires an assessment of the unmet needs of the population for which the market covers. To do this, the constraints of current options must be assessed and potential technological developments evaluated for their ability to address gaps in the market.

Reconstruction is critical in patients with soft tissue defects (Figure 1) due to cancer, trauma, deep burns, and congenital abnormalities. Viable options for these patients are lacking and in many circumstances aren't available for specific deficits. Current procedures include the use of synthetic and natural implant materials, tissue-flap grafting, and small volume fat grafting, all of which have drawbacks. Optimizing fat grafting, which uses autologous adipose tissue for reconstruction of soft tissue deficits, is a growing area of technology research which has the potential to expand treatment options and open new markets.

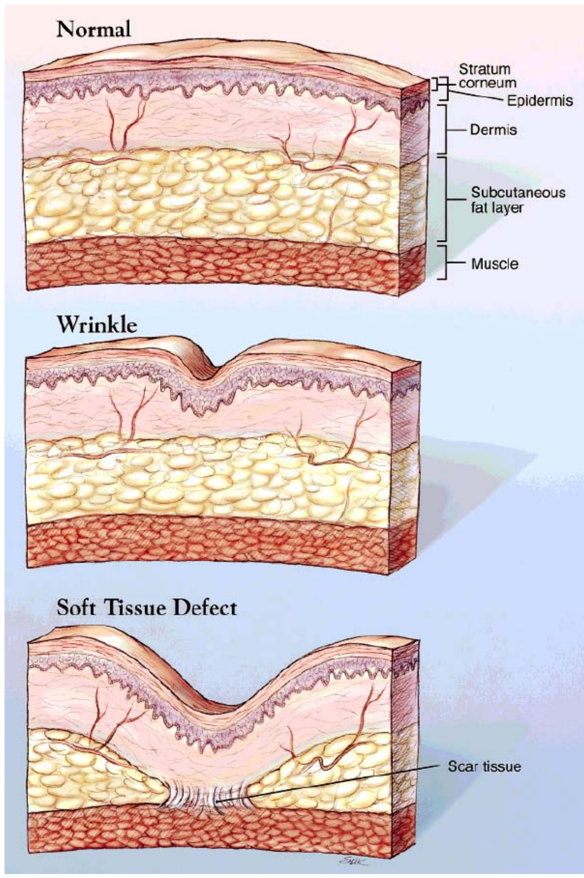


Figure 1: Depiction of a Soft Tissue Defect. Adapted from [4].

Synthetic and natural materials are used to fill the tissue-deficits; however, they do not restore function and cannot be used in all soft tissue reconstruction applications. Additionally, these materials can cause allergic reactions, side effects, infection, and fibrous tissue formation. Though there have been advances in materials development, there are still many problems associated with their clinical efficacy.

Another contemporary practice for the reconstruction of soft tissue deficits is flap grafting. This procedure uses a section of the patient's skin, fat, and muscle from a donor site, typically the abdomen, thigh, buttocks, or back, and grafts it in the area of the soft tissue deficit using microsurgical techniques (Figure 2). These highly specialized techniques are very costly in both time and money and require microvascular-surgeons. Availability and reimbursement for this type of reconstruction is rare. Additionally, the flap donor site is left with a deficit and usually a loss of function due to the removal of muscle. While this procedure eliminates some of the pit-falls of implantable materials by using a patient's own tissue, it has significant drawbacks.

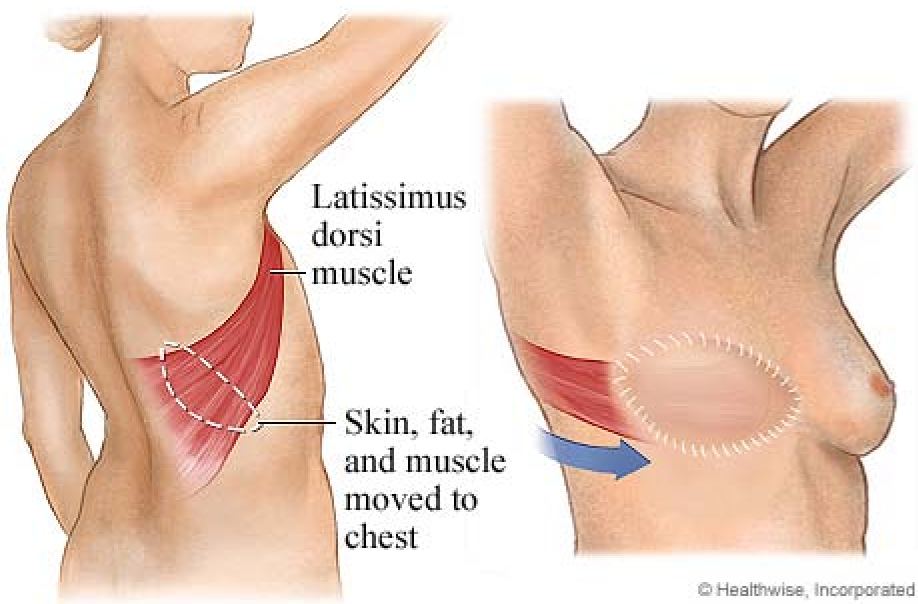


Figure 2: Flap graft illustration for breast reconstruction.

Clinics are evaluating the use of fat grafting alone or in combination with implantable materials for reconstructive and cosmetic surgeries [1, 2]. These techniques use a patient's own fat tissue to fill soft tissue deficits and therefore avoid most of the problems associated with synthetic and natural material implants. Additionally, this process can be applied to a wide variety of soft tissue defects with various shapes and volume deficits. The most common process uses adipose tissue obtained from liposuction that is then injected into the recipient site during several procedures, generally two to five, to make up for the 40-60% graft volume loss after each procedure [2]. This volume loss has been attributed to the lack of vascularization, or vessel in-growth, into the grafted tissue. Only small volumes can be maintained by the surrounding vessels because fat cells require immediate nutrition (within hours) from the blood supply to survive [3]. Therefore, this limitation will have to be overcome to make fat grafting a leading option in soft tissue reconstruction.

There are patients with soft tissue deficits that do not have appropriate treatment options due to the limitations of current practices in reconstructive procedures described above. Patients undergoing lumpectomies, a partial removal of the breast, or extremity tumor resections (Figure 3,left) are not ideal candidates for implants or flap grafts. For example, the 18 year old female, shown in Figure 3, right, was born with Poland's Syndrome, a congenital defect that prevents normal development of the pectoral muscle and associated soft tissue of the chest. Due to the tissue deficit of the chest muscle, an implant would not result in an ideal symmetrical cosmetic outcome.   Therefore these types of patients require new, clinically practical technologies to address their needs.

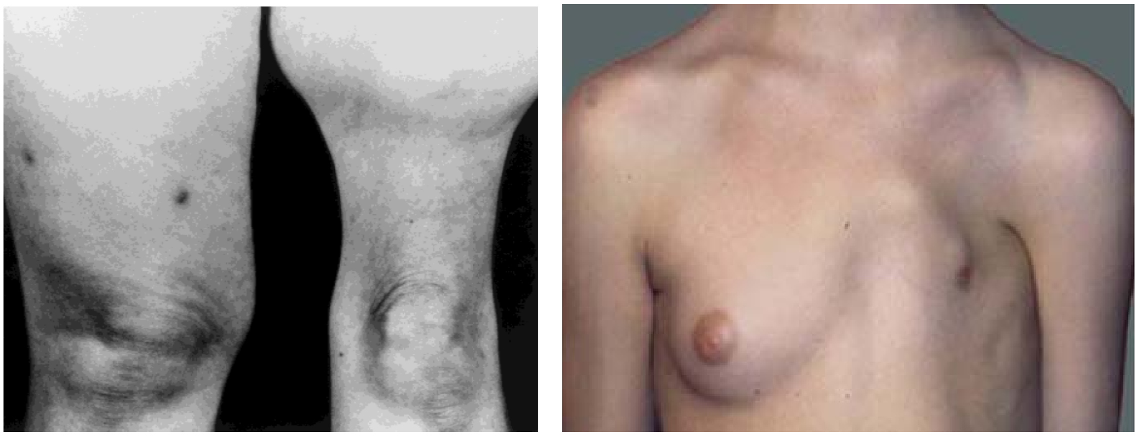


Figure 3: Left – 38 year old female 34 years after radiation treatment of a tumor. Adapted from [1]. Right – 18 year-old female with Poland's Syndrome. Adapted from [2].

Adipose tissue is an ideal material for soft tissue augmentation. It is ubiquitous in the human body, is the most abundant tissue, and is generally in excess within the patient [4]. Adipose tissue is inexpensive, readily available, easy to acquire, lacks an inflammatory or immune response, and lacks late appearing side effects or complications [5]. However, its clinical use as a graft is fraught with problems and limitations. The graft is not long lasting once transplanted and the results are varied and hard to predict. It is unknown how to overcome the onerous time, cost, and technique dependence requirements of fat grafting. Therefore, much work must be done to turn this ideal material into a practical, clinically usable solution.

The field of tissue engineering emerged to address limitations using autologous tissues for the treatment of a variety of medical conditions. This field is generally recognized for advances in combining cells, biomaterial scaffolds, and modulated microenvironments into fabricated grafts that mimic natural physiology of the tissue it is replacing [6]. Adipose tissue engineering, a subset of the field, emerged specifically to address limitations in soft tissue reconstruction by applying the principles of tissue engineering to adipose tissue. It has been expressed that “the employment of natural biology of the system will allow for greater success in developing therapeutic strategies” [7]. Therefore, it is important to not only understand the potential for creating entirely *in vitro* fabricated adipose grafts, but also the stimulation of the *in vivo* local environment such that new adipose tissue can form without the use of exogenous cells [8]. Though fat grafting, as currently practiced, is not adipose tissue engineering in the classical sense, manipulation of the microenvironment in addition to adipose tissue or adipose-derived stem cells with or without biomaterials are each described as adipose tissue engineering strategies. Therefore, broad research to understand adipose biology and tissue engineering applications to use, modify, and grow adipose tissue for reconstructive and cosmetic applications is ongoing and rapidly expanding.

Several important unmet needs must be addressed to successfully create a clinically practical adipose tissue engineering technology. Advances must be made to facilitate preparation of the transplant-recipient site to accept and incorporate large volume grafts, an endeavor that clearly falls outside the classic tissue engineering definition. Subsequent graft preparation and maintenance to prevent necrosis, or cell death, due to lack of vascularization and nutrient supply is also a major area of concern. If the technology incorporates the use of harvested fat or adipose-derived stem cells, harvesting and storage procedures needs to be optimized due to the labile nature of adipose tissue. Significant cell damage can lead to low graft take and side effects, such as cyst formation when adipose tissue is not handled or prepared properly.

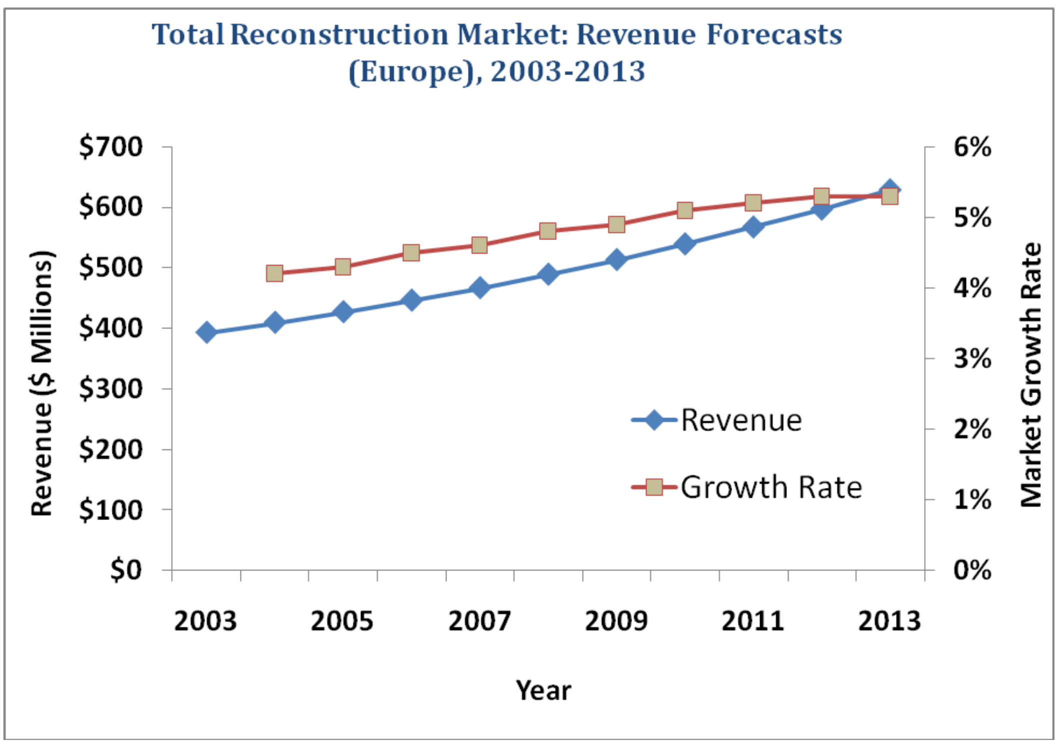
Understanding how to handle, prepare, and enhance vascularization of adipose tissue before and after transplantation will significantly impact success.

To fulfill the potential for the application of adipose tissue engineering in reconstructive surgery, it is important to fully understand where it fits in the current market. An assessment of market drivers and constraints will provide information about current unmet needs and how they could be addressed by the introduction of adipose technologies as clinically applicable solutions. Additionally, these technologies could then be adjacently applied to the cosmetic procedure market to address additional unmet needs and growing constraints. Market dynamics, potential opportunities, and new technologies are inter-related and need to be evaluated and pursued as a focused and integrated program of developing innovative technologies for the reconstructive and cosmetic procedure markets.

MARKET OVERVIEW

Reconstructive Surgery

Reconstructive surgery refers to surgical procedures to restore the appearance and function of a damaged part of the body. This market currently includes breast reconstruction, mainly in the area of mastectomies and repair of congenital defects, extremity reconstruction related to trauma, wound defects, tumor resection, and facial reconstructive surgeries. The current global reconstructive market is estimated to exceed $1 billion annually. Additionally, the market for reconstructive surgery is predicted to grow and in the case of Europe, market growth is accelerating (Figure 4).



Compound Annual Growth Rate (2006-2013): 5.0%

Figure 4: Reconstruction Revenue Forecasts (Europe), 2003-2013. Adapted from [9].

During 2009, nearly 5 million reconstructive procedures were performed in the United States, over 3.5 million of which were due to tumor removal, up 5% from 2008. These procedures are frequently intended to restore aesthetics or reconstruct natural appearance and feel [10]. The following table includes the top five reconstructive procedures according to the 2009 statistics in the American Society of Plastic Surgeons (ASPS) 2010 Report [11]:

Procedure	**Number of Procedures**
Tumor Removal	3,900,000
Laceration Repair	332,000
Scar Revision	171,000
Hand Surgery	110,000
Maxillofacial Surgery	90,000

Table 1: 2009 Statistics of Reconstructive Surgeries [11].

Breast and extremity reconstruction post tumor removal are large reconstruction markets. A Frost & Sullivan report on the Reconstructive Surgery Market in Europe states that breast and extremities reconstruction markets are experiencing small to moderate growth. There are many market drivers responsible for the growth. However, there are also several market constraints, primarily based on the current technologies available to the market. Therefore, if there were more options in the reconstructive market, such as clinically practical adipose tissue engineering technology, additional growth of these markets could be facilitated.

Breast Reconstruction

The high incidence of breast cancer is a prominent driver for the breast reconstruction market (Figure 5). Currently there are over 5 million breast cancer survivors world-wide [9]. These women typically undergo mastectomies or lumpectomies as part of their treatment causing either a total or partial loss of the breast. The psychological impact from the change in appearance of the patient's body is a large driver for reconstructive surgery. Insurance companies traditionally have considered breast reconstruction an elective cosmetic procedure. However, today there is an increasing trend toward reimbursement making reconstruction more available to those who need it after cancer treatment.

Figure 5: Breast Reconstruction Market Drivers. Adapted from [9].

There has also been an increase in early detection facilitated by new technologies, public education, and better access to screening thanks to new congressional laws. As a result, nearly 60% of patients will choose a lumpectomy procedure over a mastectomy [9]. Currently, this is considered a constraint on the market because the available reconstructive options are largely limited to whole breast saline or silicone implants. It is difficult to treat the wide variety of soft tissue deficits resulting from lumpectomy procedures and as a result there are very few reconstructive options for these patients. However, this need could turn into a very large market driver for adipose tissue grafting.

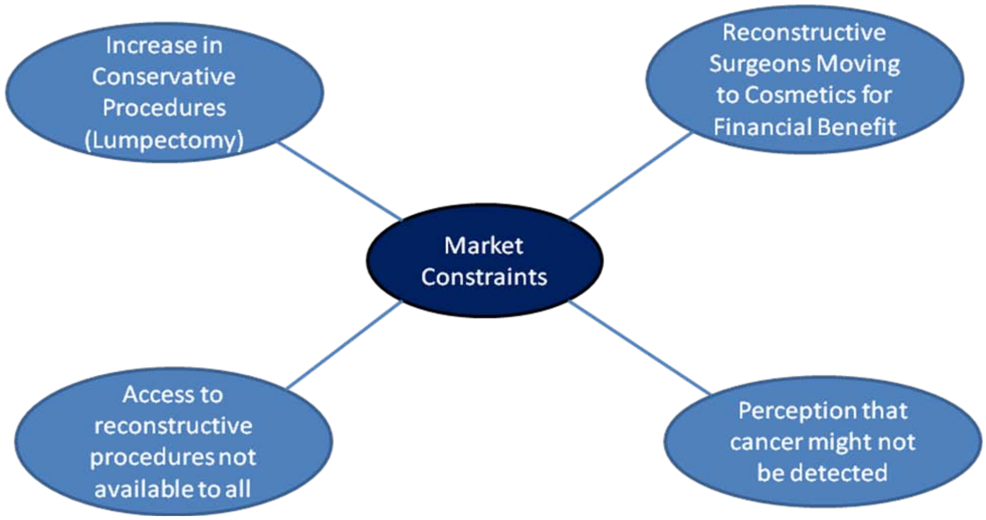


Figure 6: Breast Reconstruction Market Constraints. Adapted from [9].

Another constraint on the current reconstructive market is the perception that cancer might not be detected if the area is reconstructed, particularly where synthetic materials and implants are used (Figure 6). It is thought that implants could hide suspicious lesions or rupture during screening [9]. However, if fat grafting were a viable option for reconstruction after tumor removal, it may modulate some of these fears. The grafted tissue would be from the patient's body and incorporate into the tissue of the affected area, unlike implants. This could make the patient feel more comfortable with future cancer screening. Therefore, though this is a constraint for the current reconstructive market, it could be a driver for a market that included viable fat grafting or tissue engineering options.

There are other market restraints for breast reconstruction, which perhaps could apply to reconstruction in general. Reconstructive surgeons are increasingly moving toward cosmetic procedures due to the financial benefit associated with the private payer cosmetic procedure market. This is a difficult issue that will have to be addressed by government, society, and insurance companies. Additionally, there is often limited access to reconstructive options in general due to the shortage of reconstructive surgeons, lack of all-inclusive health insurance, and sometimes even the patient's location.

Extremity Reconstruction

Extremity reconstruction is a large area of the market that could be significantly impacted by advancements in adipose tissue engineering and fat grafting. The types of soft tissue deficits in the extremities are similar to lumpectomy patients in that they do not have many reconstructive options, particularly options with good cosmetic outcomes. Therefore, this is not only a growing market, but one with the potential for even larger growth should adipose tissue engineering produce widely available technologies.

There are many factors driving the extremity reconstruction market (Figure 7). One of the most significant includes increased life expectancy. With advanced age comes increased risk of diabetes, arthritis, and cancer, all of which contribute to soft tissue deficits in the extremities. Bone cancer, particularly in young adults, is being treated with conservative procedures sparing whole extremity amputations and creating a greater need for reconstruction. Similarly, casualties in the Iraq and Afghanistan wars have contributed significantly to this market. Again, conservative procedures are being practiced where possible, creating more need for reconstruction of damaged extremities. Additionally, there has been an increase in sports-related injuries worldwide leading to the need for reconstructive surgery, particularly in the younger generations [9]. All of these health related contributors increase not only the need for reconstruction, but also for advancements in the market to fully address both functional reconstruction and appearance.

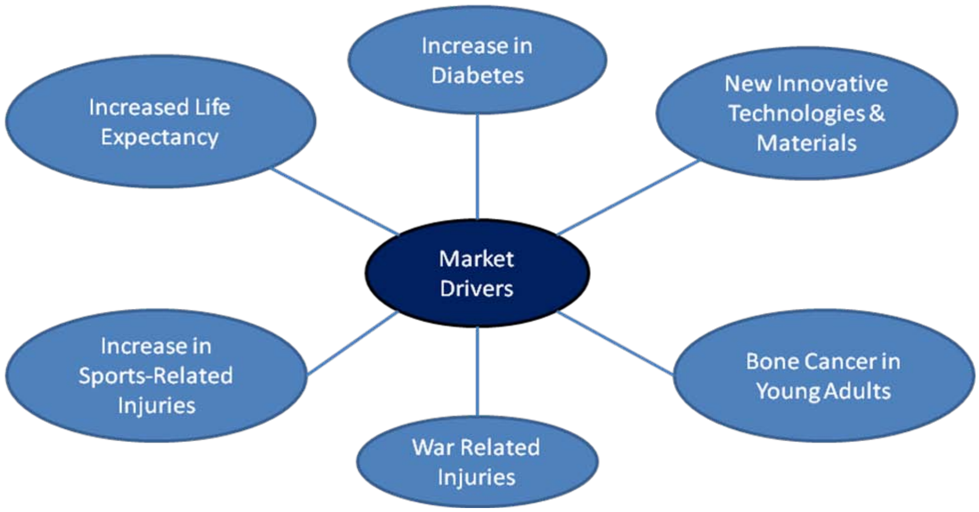


Figure 7: Extremity Reconstruction Market Drivers. Adapted from [9].

Continued innovation and introduction of new technologies and materials is also driving the reconstructive surgery market. Though there has been much research evaluating biocompatible and biomimetic materials for use in reconstruction, there are unmet needs in this area as described previously. This major driver could especially be impacted by new developments and innovation in the area of adipose tissue grafting.

Though the market is growing and there are a number of drivers, there are still some constraints on the market (Figure 8). Namely, reimbursement for extremity reconstructive surgery is not widely available as it is viewed as cosmetic, particularly when appearance is primarily affected. The large thigh defect depicted in Figure 3 is a classic example. Additionally, advances in car design, such as airbags and seatbelts, have reduced the number of traumatic injuries resulting from accidents.

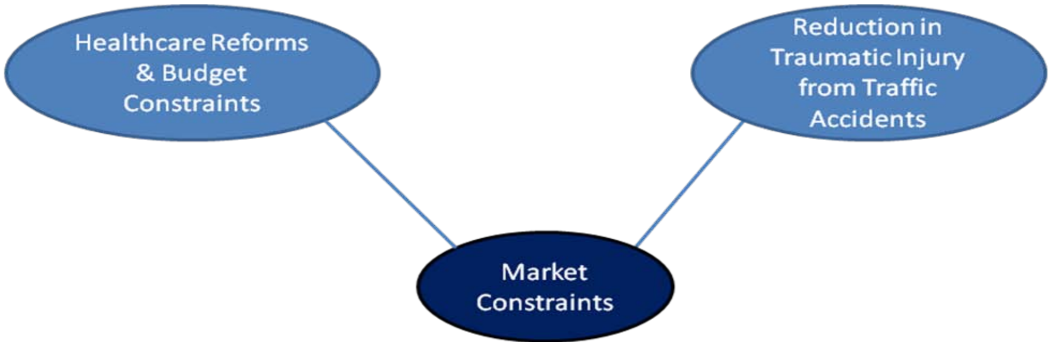


Figure 8: Extremity Reconstruction Market Constraints. Adapted from [9].

In summary, the reconstructive surgery market is growing and has significant potential for increased growth if current unmet needs are addressed. Adipose tissue engineering has the potential to greatly impact and augment this market. Though there are several constraints, there are an even greater number of opportunities for technology development and market innovation.

Cosmetic Surgery

The reconstructive surgery market is closely linked to the cosmetic surgery market. Whereas reconstruction is done to repair the appearance or function of a deficit, cosmetic surgery uses similar procedures purely to alter or enhance the body. The global cosmetic procedure market is estimated to be $30 billion annually with a compound annual growth rate of 25% [12]. This growth rate can be attributed to not only health issues related to increased life expectancy, but also to societal pressures and the desire to look young. Additionally, the expense of these procedures is borne solely by the patient as insurance reimbursement is not available. Because the cosmetic and reconstructive markets rely mainly on similar procedures, technologies, and materials, any new technology developed using adipose tissue engineering would impact both markets. For these reasons, the cosmetic surgery market is a very attractive market offers sustentative growth opportunity in addition to reconstruction.

According to the American Society for Aesthetic Plastic Surgery (ASPS) 2006 statistics, during 2006, there were 11.5 million cosmetic procedures performed. Almost 2 million of these were considered surgical procedures, while the remaining 9.5 million were classified as non-surgical, including Botox and wrinkle filling. A list of common cosmetic procedures performed that could be impacted by the development of a clinically relevant tissue engineering process can be found in Table 2 below. This table also breaks down the market size by procedure and total expenditures in the United States.

Procedure	Number of Procedures	Total Annual Expenditure
Breast Augmentation	383,886	$ 10.4 Billion
Buttock Augmentation	2,556	$ 12 Million
Cheek Implants	18,920	$ 13 Million
Liposuction	403,684	$ 956 Million
Soft Tissue Fillers		
1. Autologous Fat	96,570	$ 140 Million
2. Other Fillers	1,875,569	$ 1.1 Billion

Table 2: Cosmetic procedures with potential to benefit from an innovation in autologous fat grafting. 2006 US statistics [12].

Like any market, there are both drivers and constraints in the cosmetic surgery market. However, from the predicted growth of 25% annually, it is obvious that there are many more market drivers. These drivers can be further categorized by their impact on the market, ranging from low impact to high impact (Figure 9).

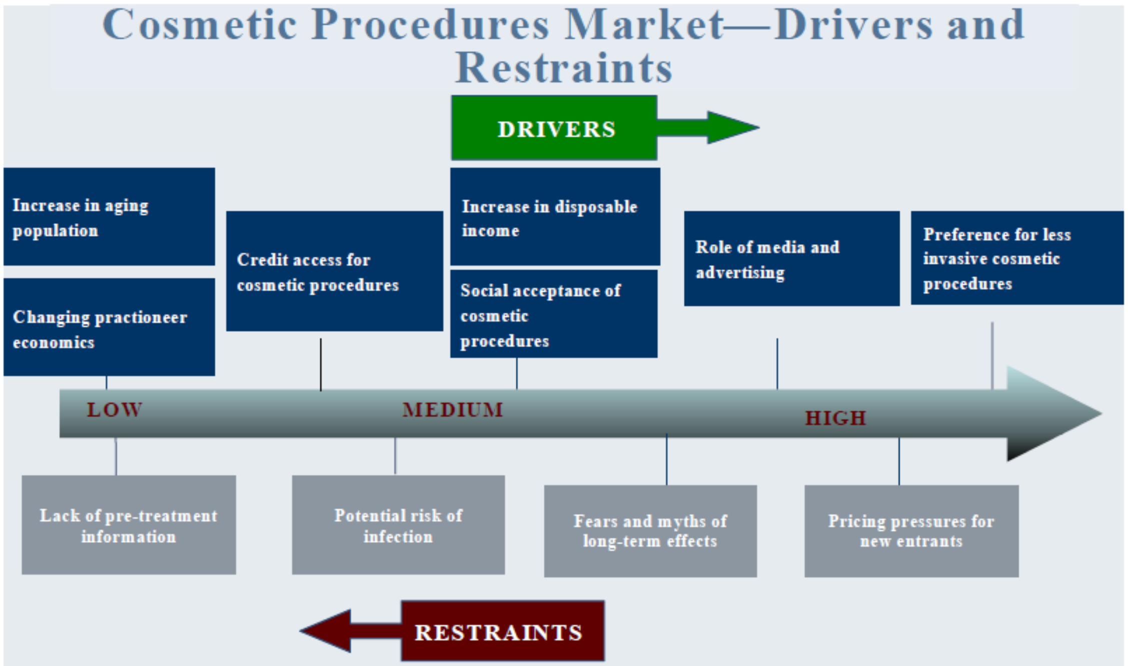


Figure 9: Cosmetic Procedures Market Drivers and Restraints [13].

Low impact market drivers include the increase in the aging population, changes in practitioner economics, and the fact that cosmetic procedures can now be financed. As mentioned previously, the societal drive to maintain looking young and healthy has a significant impact as life expectancy increases and people are more active at an older age. Plastic surgeons are increasingly choosing to focus on cosmetic procedures instead of reconstructive. This allows practitioners more flexibility for charging customers, making use of payment plans and credit lines. This availability and flexibility makes a market that once only catered to high society much more available to the general public.

Societal changes have added significant market drivers as well. There is an increase in disposable income and better acceptance of cosmetic procedures. This can be largely attributed to the role of media and advertising glamorizing cosmetic augmentation. This coverage has made this market part of everyday life, which drives more people, who once may have thought it taboo, to feel more comfortable getting cosmetic work.

One of the most significant drivers for the cosmetic market is the development of less invasive procedures with good cosmetic outcome. This can explain the wide adoption of Botox over wrinkle fillers in the past few years. Therefore, new entrants in the market must consider invasiveness of the procedure thoroughly when developing new technologies. Acceptance of new procedures or technologies will be significantly impacted by this driver and therefore if they require invasive procedures (i.e. surgical), the cosmetic result must be perceived as having better results than anything else on the market.

The constraints on the market are mainly procedurally related and include lack of pre-treatment information, potential risk of infection, and fears about long term effects. These issues could be addressed by the introduction of adipose tissue grafting as a viable option, particularly reducing fears of long term effects since it uses a patient's own tissue. Pre-treatment information and risk of infection must be addressed by the practitioners in relation to the specific procedures. However, technology innovation and clear marketing strategies could help alleviate these constraints as well.

The most significant constraint is the competitive nature of the cosmetic procedure market. Several major players dominate the market with high volumes, so pricing constraints are not as great an issue for them. However, to enter the cosmetic market the pricing must still be competitive, yet pricing strategy with lower initial market penetration must be carefully planned to make a successful entrance. Therefore, due to the competitive nature of the industry for new entrants, it would be best to fully develop and characterize new technologies within a different market, such as reconstruction. This will enable a stronger position when entering the large and competitive cosmetic surgery market.

TECHNOLOGY LITERATURE REVIEW

Current Clinical Practice

Methods currently used for soft tissue deficit reconstruction include transplantation of whole tissue flaps, implants or injection of fillers, and fat grafting. The choice to use one over the other is dependent on several factors, including severity of the defect, cost of the procedure, and access to the appropriate experts. Table 3 lists advantages and disadvantages of each treatment.

Current Strategy	Advantages	Disadvantages
Autologous Flaps		
Free Flaps	Autologous sources reduce host immune response Increased biocompatibility	Transplant Efficiency Micro-surgery is time intensive & costly
Perforator Flaps		Long-term stability Donor-site morbidity
Commercially Available Materials		
Decelularized Tissue (ECM/Tissue Components)	Act as filler for soft tissue defects Provide short-term solution	Mechanical integrity Fibrous capsule contraction
Minerals/Vegetable oils		Volume loss with time
Paraffin		
Synthetic polymers		
Silicone		
Fat grafting		
	Autologous source reduces host immune response	Volume Loss with time
	No donor-site morbidity Generally plentiful tissue Less invasive surgery	Requires multiple sessions

Table 3: Current Practices in Soft Tissue Reconstruction. Adapted from [14].

Autologous Flaps

Difficulties in primary closure of large defects, especially immediately following large tumor resections, can be overcome by reconstruction using vascularized tissue transplantation, also known as autologous flap grafting [15]. The use of whole-tissue flaps requires microvascular surgery to reconnect the blood supply from the surrounding tissue with the graft. This prevents the interruption of blood flow and thus results in a relatively stable volume transplant. The fact that the tissue is moved from one place on a person's body to reconstruct the defect increases its biocompatibility and generally restores both volume and function.

There are two types of flap procedures; free tissue and perforator (or pendulum) flaps. Free flaps are full thickness tissue grafts taken from one area of the body, completely disconnected, and transplanted to the defect site. Perforator flaps, on the other hand, preserve vascularization and nerve connections by harvesting only skin and subcutaneous fat while the underlying muscle is split, leaving a pendulum-like connection when rotated [16]. The main advantage of perforator flaps is the reduction of donor morbidity because part of the vasculature and nerve system remains connected [16]. However, local perforator flaps sometimes do not provide adequate coverage, especially when surrounding areas were also subjected to radiation. Therefore, free tissue transfer is often the most viable option.

The transverse rectus abdominus myocutaneous (TRAM) flap is the primary choice for autogenous-tissue breast reconstruction and is performed as a free flap procedure [16]. Another common harvest area includes the latissimus dorsi flap and is commonly performed using the pendulum technique described above. There is a 96% success rate for this type of reconstruction, making it one of the premier choices for reconstructive surgery [17].

However, flap procedures have significant disadvantages and limitations as well. The procedure requires highly specialized microvascular-surgeons to reconnect all of the vasculature in the flap to maintain its viability after transplant. Accordingly, this is also a very costly and time consuming procedure. In the current era of managed care, expensive procedures are often targeted in cost-containment efforts. Although microvascular tissue transfer procedures are costly, they are effective, which may ultimately decrease the cost of caring for these patients [18]. There is also significant scaring and donor site morbidity associated with the surgery, generally leaving a noticeable secondary tissue deficit to replace the tissue in the reconstructed site [14]. All together, these limitations are generally what cause patients to seek less invasive and less expensive alternatives such as implants, fillers, and fat grafting.

Commercially Available Materials

The most common reconstructive surgery method includes the use of commercially available natural and synthetic implants. Natural implant materials include decelularized dermal tissues, such as Lifecell's Alloderm™ product. Synthetic materials are comprised mainly of silicones, mineral oils, and other various polymers. Natural implants can be used on their own or in combination with synthetic implants depending on the state of the site to be reconstructed and preference of the surgeon. More commonly, synthetic fillers are used alone to replace the volume of the deficit. The advantage of using these materials as opposed to microvascular surgery is that there is no secondary surgery site for donor tissue. To be a viable option, however, the tissue surrounding the site of reconstruction must be healthy enough to accept the implant, which is often not the case for radiated tissues immediately following tumor resection. Additionally, synthetic materials only replace volume, not function and they are also associated with several side effects such as mechanical failure, volume loss over time, shifting over time, as well as fibrous capsular contraction.

Fat grafting

Fat grafting uses liposuction aspirate from one area of the body to fill deficits in another area of the body. It is not a simple procedure and should be performed only by well-trained and skilled surgeons [2]. It has gained popularity in recent years as an alternative to flap grafting and implantable fillers because it has the capacity to replace volume and function using autologous tissue without extremely costly microsurgery or significant donor site morbidity issues. There are three main components to fat grafting; tissue harvesting technique, storage, and graft volume maintenance.

The first step in fat grafting is harvesting the fat tissue and preparing for transfer such that the graft will be sufficiently healthy to live and maintain graft site volume. It is believed that liposuction results in up to 90% damaged cells [4]. However, these results vary greatly and are particularly sensitive to surgeon technique and available equipment. Additionally, it has been hypothesized that the failure of adipose grafts is largely the result of damage inflicted to the microvasculature during harvest [20]. It is believed that to help with these problems, vasoconstriction before extraction can help tissue maintain viability through reduced bleeding [21]. Though there are several recommendations by various surgeons sharing aspects of their expertise this is still an area that requires optimization to help improve fat grafting as a reliable reconstructive technique.

Once tissue is harvested, it can either be injected immediately or stored for additional injections. It has been found that slow freezing of the tissue shortly after harvesting is an effective method of maintaining cell viability [21, 22]. It is recommended that cells be stored less than 6 months, although viable cells have been found in samples stored up to three years [21]. Storage of fat grafts allows for multiple grafting sessions with only a single harvest, reducing patient discomfort, cost, and time spent by both patient and physician [22].

The final step of fat grafting is injecting into the deficit. The graft should be handled with gentle manipulation and placed in a vascular, tension-free recipient bed [1]. Additionally, it is well known that fat transplanted into muscular or subcutaneous tissues survives well due to the rich blood supply compared to tissues such as the retroglandular plane where there is not much vasculature [1, 20]. This increases the chance of adipocyte survival and integration with the surrounding tissue. The literature indicates that major complications associated with fat grafting are mainly attributed to technical errors and selection of the wrong anatomic site for both harvesting and injection of the fat [2].

Results of fat grafting are highly dependent on surgeon technique and expertise. Additionally, there is a relative lack of information to guide physicians in choosing best practice techniques, selecting appropriate patients, and offering realistic advice on outcomes and potential complications [19]. For this reason, the ASPS Task Force developed an evidence-based review offering surgeons a graded summary of the literature to help optimize the clinical use of fat grafts as currently practiced. In summary, they found that though there is a great deal of variability in techniques and subsequent results, fat grafting can be considered a safe method of augmentation and correction of defects associated with various medical conditions. In addition, the current trend in medicine is toward less aggressive methods compared to free tissue transfer reconstruction of complex wounds [16]. Therefore it is important to understand the components and limitations of fat grafting as practiced to make it more predictable and repeatable.

Though fat grafting is becoming more prevalent due to the advantages previously described, the main drawback is volume loss and consequently the requirement for multiple sessions to fill larger deficits. The ASPS Task force review of human case study literature found that graft volume loss via reabsorption or necrosis is the primary cause of poor results. On average, there is a 40-60% reduction in graft volume using liposuction aspirate following transplantation, requiring surgeons to overfill and patients to sit through multiple grafting sessions over a period of several month [4]. Additionally, due to the high resorption, some surgeons have tried using excised intact fat pads as opposed to liposuction aspirate. Several studies have demonstrated that the resorption rate was higher for aspirated fat compared with excised fat or harvested fat cylinders [1]. They proposed that to maintain adipocyte viability and subsequent graft survival, the capillary structure of the transplant should be preserved [1]. No matter the technique or type of fat grafted, currently there is no way to use this method on large deficits and obtain the desired result with just one procedure.

Illouz *et. al* also described several case study results in breast reconstruction and cosmetic augmentations using autologous fat grafting. They have practiced this procedure for over 25 years with predictable and satisfying results based on the condition that the treatment is performed in stages with small quantities of adipose tissue fat injected in each treatment session. At each session, 25-180 cc of fat was grafted into each breast with the number of sessions ranging from one to five. The total amount of fat transplanted in each breast ranged from 25-900 cc. Though the results achieved in these case studies were quite natural in appearance and clients were very satisfied, volume limitations still exist, requiring multiple session treatments for desired results.

It is widely accepted that patients who have underdone irradiation are not good candidates for breast alloplastic reconstruction because of the high rate of complications. Therefore, Salgerello *et. al.* described two case studies where patients post-radiation of the breast following breast cancer received two sessions of fat injections before implant placement to improve the compliance between implant and irradiated tissues. They encourage autologous reconstruction alone or combined autologous and alloplastic reconstruction in irradiation patients because the autologous fat helps restore the local tissue from the radio-damage and allows for safer placement of the breast tissue expander/implant.

In a post-radiation thigh defect case described by Jackson *et. al.,* four grafting sessions were required to achieve a desired result. The first session injected 80cc of fat harvested from the abdomen, 140cc at the second session, and 200cc during a third session at eight month intervals and a final injection of 140cc eleven months later.

Through this 30 month year period, significant improvement in the massive circumferential defect was made, though the results were still not to a completely natural state. This ultimately showed, however, that viable fat cells can be transplanted and survive in adverse environments such as post-radiated tissues.

Due to the significant advantages with using autologous fat transplantation, it appears to be the most favorable reconstructive option. However, since current clinical defect reconstruction requirements are typically on the order of cubic centimeters, a more viable alternative to the multiple session treatments is required. Therefore, a way to combine the benefits of fat grafting with a method of maintaining viability of constructs of significant dimensions would be of great clinical benefit.

Adipose Tissue Engineering

To address the limitations of fat grafting, the field of adipose tissue engineering (ATE) has emerged. This field endeavors to offer novel solutions and tissue engineering strategies to incorporate cell sources, biomaterial scaffolds, and a microenvironment to provide the appropriate cues and signals for growth and tissue formation [14]. To be successful for use in reconstructive applications, an adipose tissue construct must define and maintain a three-dimensional volume following implantation [23]. Additionally, the bioactivity of the regenerated adipose tissue needs to mimic that of native adipose tissue, not only in function, but in structure, which includes the incorporation of functional vasculature comprising blood vessels, nerves, and lymph supply [14]. Adipose tissue that both possesses active metabolic function and maintains volume after implantation would serve as a significant advancement over other reconstructive options.

One tissue engineering strategy for adipogenesis includes making use of transplanted, possibly tissue culture expanded, stem cells with high potential for proliferation and differentiation to achieve *in vitro* cell-induced regeneration. An alternative strategy involves inducing *in vivo* formation of adipose tissue by making use of stem cells, like preadipocytes, already present in the body [8]. The following sections will describe the biology of adipose tissue, adipose derived stem-cells, vascularization, microenvironment, substrate materials, and the combination of these components for application in these adipose tissue engineering strategies as described in the literature.

Biology of Adipose Tissue

Adipose tissue is ubiquitous in the human body and is the most abundant tissue in the body [4]. The primary cellular component of adipose tissue is a collection of lipid filled cells known as adipocytes (Figure 10) that are held in place by collagen fibers. Other cellular components in adipose tissue include smooth muscle cells, endothelial cells, fibroblasts, blood cells, and preadipocytes [24]. Adipose tissue is highly vascular with each adipocyte attached to at least one capillary [4]. In fact, approximately 20% of the volume of native subcutaneous fat is vascular tissue [10]. Close interaction with the capillary network is required to sustain the high metabolic rate of mature adipocytes.

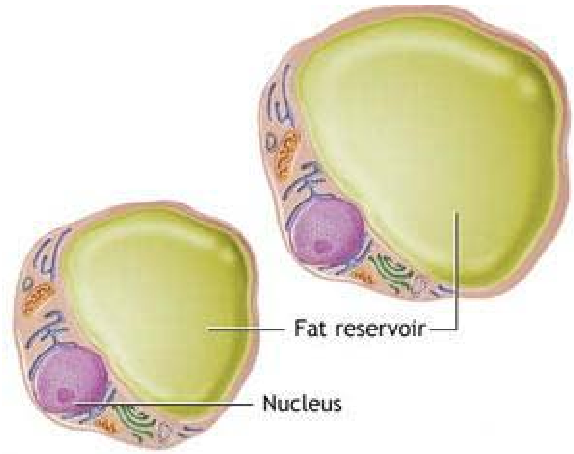


Figure 10: Representation of adipocytes (fat cells).

Fat cells are fragile due to their structure and function, which must be considered when developing the methods for harvesting, storage, grafting, and use in tissue engineering applications. The harvesting method must consider the large lipid content, which makes the cells easy to rupture, as well as the impact on the integrity of the vascular structure within the tissue. Additionally, storage, treatment, and placement of the excised tissue, or graft, must also consider these characteristics of adipose tissue, particularly the requirement for immediate blood supply.

Adipose tissue also contains mesenchymal stem cells within the adult tissue, which are beneficial in tissue engineering applications. It was once thought that bone marrow contained the largest proportion of these cells, but it has recently been discovered that adipose tissue contains up to 1000-fold more, 2% as compared to 0.002% in bone marrow [25]. Mesenchymal stem cells (MSCs) are interesting due to their ability to differentiate into adipose tissue, endothelial (blood vessels) and bone tissue (Figure 11). Additionally, adipose-derived mesenchymal stem cells are known to secrete angiogenic and anti-apoptotic cytokines, growth factors, and extracellular matrix material that support tissue regeneration, enhance angiogenesis, and reduce tissue damage [4, 25].

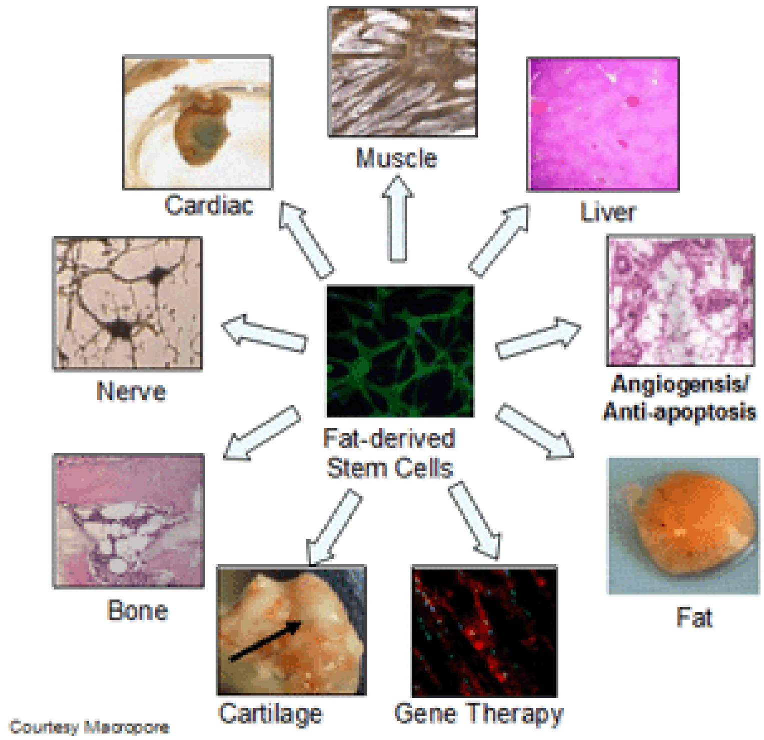


Figure 11: Differentiation Capability of Fat-derived Stem Cells.

Ongoing research has the potential to answer questions about the optimal methods to work with adipose tissue, how to stimulate vascularization, how to induce adipose derived stem cells to differentiate into blood vessels, and many others to address the limitations of fat grafting.

Vascularization

The application of adipose tissue grafting requires further research to engineer a clinically practical solution for large tissue deficits. Currently, only small volumes fat-grafts succeed because nutrients are supplied through simple diffusion due to the lack of an intact vascular network. For this reason, large volumes are observed to necrotize, or die, rather quickly after implantation due to the lack of vascular blood supply. Diffusion can supply cells only over a distance of 150-200µm, insufficient for larger constructs [3]. Vessels from the surrounding tissue grow into the transplanted tissue after a delay of several days, up to two weeks, and even then only nourish the periphery of the graft [3, 4, 20]. By this time, up to 60% of the tissue is lost to necrosis. To overcome this limitation, research must focus on accelerating vascularization. Figure 12 is a depiction of vascular growth into a large volume fat graft. It is this process that must be sped up to address volume loss currently associated with fat grafting.

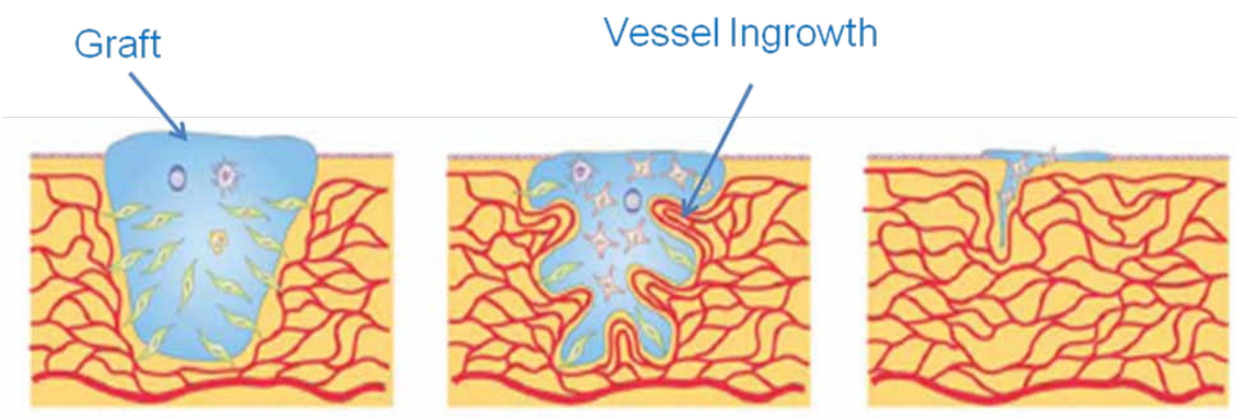


Figure 12: Depiction of vascularization into graft (Adipose Transplant, Scaffold, etc.).

Sufficient functional vasculature is vital for the construction of large constructs in which nutrients and oxygen diffusion is limited by distance and metabolic needs requiring immediate integration of vessels [14, 20]. Therefore, any potential clinically translatable tissue engineering modality must consider the microvasculature [1, 3, 4, 14, 22, 24, 27]. Consequently, stimulation of vascularization is a growing area of research with much interest because of its essential role in tissue engineering.

There have been several studies evaluating co-transplanting endothelieal cells (EC), mesenchymal stem cells, or even partial vessel constructs along with adipose tissue [3, 20, 28]. Cotransplantation of autologous ECs to aid in the formation of a capillary network within the graft immediately after transplantation could result in a sufficient homogenous supply of the whole graft [3]. Other studies have evaluated the effect of growth factors and other hormones such as insulin on vascularization of new grafts [20]. The application or stimulation of endogenous growth factors may contribute to improvements in vascularization of transplanted fat because ischemic fat grafts themselves induce angiogenic cytokines [4, 20]. Additionally, the use of structural scaffolds seeded with stem cells to maintain volume and encourage faster vascularization has been an area of interest [27, 29]. Mechanical manipulation of vessels has also been evaluated along with the chemical and biochemical processes mentioned. The evaluation of this wide array of mechanisms will contribute to the development of an optimal adipose tissue engineering process.

Microenvironment

The adipose niche comprised of adipogenic stimulants, growth factors, adipokines, and cytokines, makes up the complex microenvironment that stimulates and maintains native adipose tissue [14]. In addition to maintaining the vascular structure in the graft, there is evidence that the microenvironment of the recipient site can be manipulated to affect transplant success. Many lines of evidence show that adipocyte precursor cells distribute widely in the connective tissues of the adult body and have high potential of adipogenesis and vascularization, depending on the microenvironment [27].

Manipulation of the microenvironment in not only the recipient site, but also the graft donor site, may be key to influencing faster vascularization such that larger volume grafts are clinically feasible.

In addition to preparation of the microenvironment of grafts and donor sites, some believe it may be possible to stimulate cells with a local environment such that it is suitable for their proliferation and differentiation, resulting in *in vivo* formation of adipose tissue without exogenous transplantation of cells [8, 27]. The manipulation of these factors in surrounding adipose tissue could stimulate the influx of adipose derived stem cells therefore increasing the likelihood of neovascularization and fat formation in the stimulated area.

On the other hand, it is more prevalently believed that the true potential of adipose derived stem cells (ASC's) will be achieved by using grafts enriched with these stem cells as a transplant to aid in formation of adipose tissue and neovascularization. It is well known that mature transplanted adipocytes have already differentiated and provide little potential for further growth, so the only way to achieve potential for continued fat formation is to provide the environment with cells that have potential for differentiation and proliferation. One study confirmed that enriched fat can survive better (35% on average) than non-enriched fat, and microvascularization can be detected more prominently especially in the outer layers of the fat transfer [2].

ASC's are also much more resistant to mechanical damage and ischemic conditions than mature adipocytes making them even more ideal for optimizing fat grafting methods [28]. Additionally, their introduction alone can impact the microenvironment by secreting cytokines that support tissue regeneration and minimize tissue damage [25]. Silvia *et al.* also found that MSC frequency positively correlates with blood vessel numbers supporting the belief that utilizing the potential of these stem cells will help address the issue of slow vascularization in fat grafts.

Despite recognition of the potential for adipose derived stem cells there are still several concerns to address, including standardization of methods for procurement, cell isolation, identification, and cell culture [24]. Additionally, it is also believed that using undifferentiated MSCs in patients may be problematic because MSCs may undergo malignant transformation over time [10]. These concerns must be addressed to be a clinically applicable option for adipose tissue engineering. There would be great value in being able to stimulate *in situ* migration of ASCs to the site of a large tissue defect to encourage *in vivo* formation of new adipose tissue without the risks associated with extraction, expansion, and re-implantation.

Scaffold Technologies

Synthetic and natural materials have been evaluated as scaffolds, or mechanically stable structures, to help fill large deficits. These materials can be seeded with autologous adipose tissue, stem cells, or growth factors to provide an environment for cells to migrate, expand, and form soft tissue. The scaffold plays two important roles in tissue regeneration: it provides a platform for cells to attach and maintain life as well as provides space for tissue regeneration [8]. Therefore, the material of the scaffold must meet both aesthetic requirements while also providing surfaces that will promote cellular attachment throughout the volume of the structure.

Several biocompatible synthetic polymers have been molded into various shapes and sizes and seeded with liposuction aspirate, stem cells, endothelial cells, and even intact microvessel constructs [3, 14, 28, 29]. The most common polymers are used in many tissue engineering areas of research and applications, so their properties, degradation products, and biocompatibility are fairly well understood. Additionally, tailoring their exact composition enables the manipulation of the resulting mechanical properties and longevity. Table 4 outlines the strengths and weaknesses of the most common synthetic polymers used in adipose tissue engineering applications. The base polymers can be mixed together and/or incorporate chemical or surface modifications in an effort to modulate the mechanical properties and increase cellular and implant biocompatibility [24]. There have been various results observed regarding longevity of cell seeded scaffolds using these materials, but overall, there have been no clinically translatable constructs produced using these methods to date.

Synthetic Polymer	Strengths	Weaknesses
Poly(lactic acid)	Supports adipogenesis *in vivo* and *in vivo*	Degrade *in vivo* after 12 weeks
Poly(glycolic acid)	Supports adipogenesis *in vivo* and *in vivo*	Degrade *in vivo* after 4 weeks
Poly(lactiv-co-glycoloic acid)	Supports adipogenesis; induces vascularization *in vivo*	Long-term adipose tissue engineering studies have not been performed *in vitro* or *in vivo*
Poly(ethlene glycol)	Supports adipogenesis; maintains shape afer *in vivo* culture	*In vivo* degradation rate not well characterized
Fluoropolymers	Maintains shape	Nondegradable; unfavorable surface for cell adhesion
Silicones	Biocompatible	Nondegradable

Table 4: Common Synthetic Polymers Used for Adipose Tissue Engineering. Adapted from [14].

Similar studies have been conducted using natural polymers [10, 28]. Table 5 provides a list of examples and describes the strengths and weaknesses of these materials for adipose tissue engineering applications. These materials are thought to provide a more natural, biocompatible environment to seed stem cells, therefore, resulting in better outcomes. For example, a study using micronized decellularized (DCM) dermal matrix, in conjunction with ASC's, found that two months following implantation, the graft contained many large capillaries while injected micronized DCM alone only contained some fibroblast-like cells and a few small capillaries [28]. Additionally, DCM materials are also known to contain growth factors with strong angiogenic activity and the ability to promote preadipocyte growth [8].

Material	Strengths	Weaknesses
Adipose-derived ECM	Native ECM promotes favorable microenvironment for adipogenesis	Has not yet been formulated as a 3D porous scaffold
Collagen	Prevalent in native adipose ECM; promotes favorable adipose outcomes; well characterized	Fast degradation rate *in vivo*
Decellularized human Placenta	Allogenic approach to generate large adipose substitutes; supports adipose tissue formation	Extensive isolation and decellularization procedure (18 days)
Fibrin	Biocompatible material that can support adipogenesis *in vivo*	Has not yet been formulated as a 3D porous scaffold
Gelatin	Supports adipogenesis *in vivo;* retains shape after culture	Primarily used as material for microspheres; 3D construct for adipose tissue engineering not well utilized
Hyaluronan	Favorable mechanical properties; supports adipose tissue formation	3D porous scaffolds have not been widely successful for adipose outcomes
Matrigel	Supports adipogenesis	Cannot be used in human *in vivo* applications
Silk	Supports adipogenesis; favorable mechanical properties; slow degradation rate	Have not been utilized for long-term *in vivo* soft tissue engineering (>6 months)

Table 5: Common Natural Materials Used for Adipose Tissue Engineering. Adapted from [14].

There have also been several promising studies using intact placental decellular matrix due to its structural integrity, biocompatibility, and inclusion of growth factors [14, 23, 24]. In one study, the implant volume appeared to be maintained and contained an extensive number of mature adipocytes at 8 weeks [23]. The preservation of the implant volume is thought to be related to the complex extracellular matrix architecture of this intact decellularized tissue.

In addition to seeding scaffolds with ASC's, several other studies have evaluated the inclusion of autologous endothelial cells as well as intact engineered mircrovessels to address the immediate need for vascularization of this large tissue construct. It is thought that by providing these components, the developing capillary network may form connections more immediately to vessels sprouting in from the surrounding tissue, supplying blood to the periphery but most importantly in the graft's center [3].

Summary

A schematic provided by Charles Patrick (Figure 13) depicts an idealized scenario for adipose tissue engineering incorporating all of the components previously discussed, including the use of autologous adipose tissue, potentially enriched with ASC's, in conjunction with scaffold materials and manipulation of the microenvironment using endotheilial cells, microvessels and potentially growth factors. The key is finding the right combination of these components, externally introduced or internally induced, for the specific applications that will lead to a clinically practical solution for reconstructive surgery.

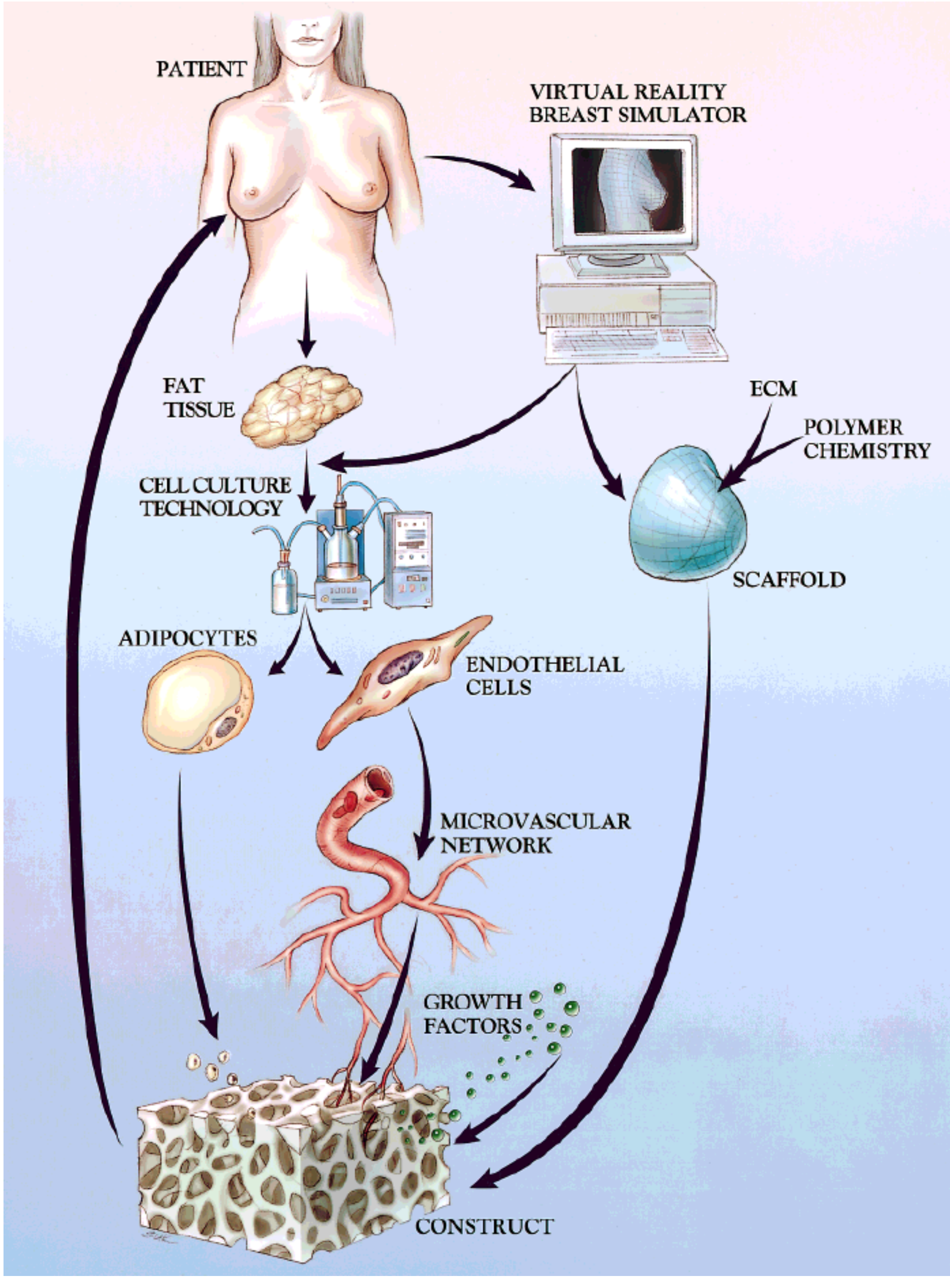


Figure 13: Schematic of proposed tissue engineering strategy for development of a de novo breast [4].

COMPETITIVE LANDSCAPE

Leading Companies & Products in Reconstructive Surgery

There are several types of breast and other anatomy-specific cosmetic implants (i.e. chin, lips, buttocks, etc.) currently on the market. However, this section will focus on the companies that are producing general soft tissue constructs that can be used for the non-specific deformities discussed in the earlier sections, including tumor resections and congenital defects, as opposed to purely cosmetic augmentation. Table 6 lists the most common filler materials used in place of adipose tissue in reconstructive surgery.

In addition to filler materials listed in table 6, surgical meshes are common product used for reconstructive surgery to reinforce soft tissues where weaknesses exist. There are over 450 devices listed as surgical meshes on the FDA 510K database. These devices support defect repair generally without filling deficits and augmenting the appearance of the area. Some of the leaders in this industry are Atrium Medical Corporation, Boston Scientific, Cook Medical Inc., Ethicon Inc., Synovis Life Technologies, Inc., and Serica Technologies. Though these companies are not currently in the market with adipose tissue alternative reconstructive filler products, they are large companies with adjunctive products in the market. Therefore, there is incentive for them to address the unmet needs in their market by evaluating the potentials in adipose tissue engineering.

Material	Product (Manufacturer)	Primary Component(s)
Extracellular Matrix/		
Tissue Matrix	AlloDerm (LifeCell Corp)	Decellularized human dermal tissue
	Autologen (Collagenesis, Inc.)	Autologous human dermal collagen
	Cymetra (LifeCell Corp)	Micronized AlloDerm
	PriMatrix (TEI Biosciences)	Fetal bovine decellularized matrix
	Dermalogen (Collagenesis, Inc.)	Allogenous human dermal tissue matrix
	Fibrel (Mentor Corp)	Fibrin Gel
	Prevelle® Silk (Mentor Corp)	Hyaluronic acid-based dermal filler
	Hylaform (Biomatrix Corp)	Hyaluonic acid gel
	Restylan (Q-Med)	Viscoelastic hylan gel
	Zyderm I (Collagen Aesthetics)	Bovine dermal collagen (35 mg/mL)
	Zyderm II (Collagen Aesthetics)	Bovine dermal collagen (65 mg/mL)
	Zyplast (Collagen Aesthetics)	Zyderm II with gluteraldehyde
Synthetic Polymers		
	Artecoll (Rofil Medical Inc)	Polymethylmethacrylate microspheres
	Bioplastique (Bioplasty, Inc.)	Cross-linked polydimethylsiloxane
	Gortex (W.L. Gore & Associates)	Expanded polytetrafluoroethylen (ePTFE)
	Marlex (Davol, Inc.)	Porous/mesh-form polyethylene
	Softform (Collagen Aesthetics)	Expanded polytetrafluoroethylen (ePTFE)
Silicone	Various Formulas (Dow Corning)	

Table 6: Materials used in place of adipose tissue in reconstructive surgery. Adapted from [26].

Up-and-coming Companies with Adipose Technologies

Cytori Therapuetics is the most publicized company with products addressing needs in the current fat grafting market with its Cellution technologies that have potential application in adipose tissue engineering strategies. Cytori's products are marketed as revolutionary technologies for harvesting, filtering, and transferring fat grafts. These technologies address some of the issues with cell viability of the liposuction aspirate by purifying it before transplantation. They are also currently working with Olympus Corporation to develop a next generation device to extract and concentrate adipose-derived stem and regenerative cells with larger tissue processing volume (www.cytori.com). Table 7 lists Cytori's FDA cleared products.

Device	**510K Intended Use**
AFT System	Aspiration, harvesting, filtering, and transferring autologous tissue
Celution Cell Concentration Device	Collection, Concentration, washing, and reinfusion of autologous cells to obtain concentrated blood cells for reinfusion
PureGraft 250-PURE System	Harvesting, filtering, and transferring autologous fat tissue for aesthetic contouring

Table 7: Cytori Therapeutic FDA approved devices for use in fat grafting and tissue engineering applications (www.fda.gov).

AestheTec is a start-up company that is reported to be developing fat grafting technologies. However, there are no approved or marketed products by this company and there is very little information available at this time describing the specific technologies on which they are working [19].

Other ATE Applicable Technologies

CryoLife has two marketed technologies that are or could be applicable to future adipose tissue engineering strategies. Their cryopreserved vascular conduit alternative products (including main arteries and veins) could be used to introduce immediate vascularity into engineered grafts. Additionally, they have a patented decellularization process in the area of cardiovascular implants. However, this type of process has wider applicability across other tissues as well, including potential soft tissue constructs similar to LifeCell technologies described above.

NOVADAQ is a company that focuses on plastic and reconstructive surgery imaging technologies. They offer the SPY Imaging System that produces real-time visual images of blood vessels in minutes. This tool could not only be used to assess blood flow in soft tissue grafts, engineered or flap graft surgeries, but could also potentially be used as a sophisticated research tool to assess up-and-coming adipose tissue engineering technologies for their successful vascularization over time in animal models and clinical trials. An example software image showcasing the capability of this technology can be found in Figure 14.

Figure 14: SPY Technology companion software screenshot (www.novadaq.com).

TECHNOLOGY OPPORTUNITIES

Due to unmet needs in the reconstructive market, including difficult reconstructive cases that currently have limited options and improvement of functional and cosmetic outcomes for other reconstructive cases, much research has been performed to help develop an adipose tissue based clinically practical solution. From a review of the literature and current technologies, it is evident that there are several technology opportunities that could lead to products to help address these unmet needs. The main objective of creating a single stage adipose graft treatment may be a long-term technology goal; however, there are several opportunities to take advantage of by combining current research with state-of-the art technologies already utilized in other applications. The main areas of focus for product technologies are as follows:

- Harvest Adipose Tissue
  - Devices, methods and/or additives to minimize graft cell damage
  - Devices and/or methods to improve isolation and/or expansion of stem cells
  - Devices and/or methods to maintain capillary structure of graft
- Improve/Speed up Vascularization
  - Prepare graft site to accept graft – increase surrounding vascularization and create space to accept graft sub-dermally
  - Stimulate micro-environments to influence *in vivo* stem cell differentiation
  - Create micro-mechanical changes to influence angiogenesis
- Maintain Volume During Graft Integration
  - Use of Decellularized Large Tissue Scaffolds
  - Prevent necrosis/apoptosis

VALUE PROPOSITION

Economical, clinically-adopted solutions equal revenue potential for businesses. To companies not currently in the market, but adjacent to it, the reconstructive and cosmetic markets are attractive and actively growing. Therefore, there is value for both the potential customers as well as businesses to evaluate technology opportunities that may help to address the increased need for better/safer cosmetic & functional outcomes as an alternative to:

- Implants: considered "good enough," but are prone to several side-effects, mainly because they are not autologous tissue.
- Flap grafting: requires microvascular surgery which is an expensive and time-intensive surgery with a high risk of donor-site morbidity.
- Fat-grafting: requires multiple sessions over a long period of time to achieve acceptable results.

New technologies should provide:

Value to the Customer (Patients & Physicians)

- Decreased Cost (as compared to flap grafting)
- Improved Functional & Cosmetic Results
- Single Procedure
- Reduced Side Effects

Value to the Business

- Strategic Expansion Opportunity (Increase Market Share)
- Leverage Existing Technologies in New Application
- Access to Cosmetic market with 25% global annual growth potential

RECOMMENDATIONS

Tissue engineering research programs are expensive, as well as time and personnel resource intensive. Therefore, strategic decision analysis should be completed to evaluate the business appetite for potentially long-term and high risk research before beginning an adipose tissue engineering program. It is recommended that a detailed business plan addressing a specific market segment (i.e. breast lumpectomy reconstruction) should be completed to help narrow the areas of research and application of resulting technologies. Furthermore, ideally, if a program is initiated to review technologies in this area, it is recommended that the short-term opportunities, especially adjunctive therapies to fat-grafting, be evaluated in parallel to some of the longer-term technology opportunities to help balance the program and ensure its longevity by creating multiple product opportunities for the market.

REFERENCES

1. Jackson IT, DS Hon, R Simman, R Tholen, and VD DiNick. A successful Long-Term Method of Fat Grafting: Recontouring of a Large Subcutaneous Postradiation Thigh Defect with Autologous Fat Transplantation. Aesthetic Plastic Surgery 2001: 25;165-169.

2. Illouz YG & A Sterodimas. Autologous Fat Transplantation to the Breast: A Personal Technique with 25 Years of Experience. Aesth Plastic Surgery 2009: DOI 10.1007/s00266-009-9377-1.

3. Borges J, MC Mueller, NT Padron, F Tegtmeier, EM Lang, and GB Stark. Engineered Adipose Tissue Supplied by Functional Microvessels. Tissue Engineering 2003: 9(6):1263-1270.

4. Patrick CW. Adipose Tissue Engineering: The Future of Breast and Soft Tissue Reconstruction Following Tumor Resection. Seminars in Surgical Oncology 2000: 19;302-311

5. Kaminer M and NE Omura. Autologous Fat Transplantation. Arch Dermatology 2001: 137;812-814.

6. Lanza RP, R Langer, & J Vacanti. (Eds.). (2007). *Principles of Tissue Engineering.* Burlington, MA, San Diego, CA, & London. Elsevier Academic Press.

7. MacArthur BD and ROC Oreffo. Bridging the gap. Nature 2005: 433(6); 19.

8. Kimura Y, et al. Adipose Tissue Formation in Collagen Scaffolds with Different Biodegradabilities. Journal of Biomaterials Science 2010: 21;463-476.

9. Frost & Sullivan. Reconstructive Surgery Markets in Europe. H025-54. September 2007

10. Or-Tzadikario S, et al. Quantitative Monitoring of Lipid Accumulation Over Time in Cultured Adipocytes as Function of Culture Conditions: Toward Controlled Apdipose Tissue Engineering. Tissue Engineering Part C. November 2010:00(00); 1-15. DOI: 10.1089/ten.tec.2009.0755.

11. American Society of Plastic Surgeons. 2010 Report of the 2009 Statistics. National Clearinghouse of Plastic Surgery Statistics.

12. American Society for Aesthetic Plastic Surgery. 2006 Cosmetic Surgery National Data Bank Statistics

13. Frost & Sullivan. Cosmetic Procedures Markets in Europe. MoF4-54. June 2007

14. Choi JH, et al. Adipose Tissue Engineering for Soft Tissue Regeneration. Tissue Engineering Part B November 2010:00(00); 1-13. DOI: 10.1089/ten.tec.2009.0544.

15. Morii T, et al. Soft Tissue Reconstruction Using Vascularized Tissue Transplantation Following Resection of Musculoskelatal Sarcoma. Annals of Plastic Surgery 2009. 62(3):252-257.

16. Chang DW & GL Robb. Recent Advances in Reconstructive Surgery for Soft-Tissue Sarcomas. Reconstructive Surgery 2000: 2;495-501.

17. Cordeiro PG, *et al*. The Role of Free Tissue Transfer Following Oncologic Resection in Lower Extremity. Annals of Plastic Surgery 1994. 33(1):9-16.

18. Heller L & SJ Kronowitz. Lower Extremity Reconstruction. Journal of Surgical Oncology 2006: 94;479-489.

19. Gutowski KA & ASPS Fat Graft Task Force. Current Applications and Safety of Autologous Fat Grafts: A Report of the ASPS Fat Graft Task Force. Fat Grafting Manuscript Resubmission. February, 2009.

20. Langer S, et al. Revascularization of Transplanted Adipose Tissue: A Study in the Dorsal Skinfold Chamber of Hamsters. Annals of Plastic Surgery 2002: 48(1);53-59.

21. Sommer B and G Sattler. Current Concepts of Fat Graft Survival: Histology of Aspirated Adipose Tissue and Review of the Literature. American Society for Dermatologic Surgery 2000: 26;1159-1166.

22. MacRae JW, et al. Ex Vivo Fat Graft Preservation. Annals of Plastic Surgery 2004: 52(3);281-283.

23. Flynn L., et al. Adipose Tissue Engineering in vivo with adipose-derived stem cells on naturally derived scaffolds. Journal of Biomedical Materials Research Part A May 2008. DOI: 10.1002/jbm.a.32044. 929-941.

24. Gomillion CT. et al. Stem Cells and Adipose Tissue Engineering. Biomaterials 2006: 27;6052-6063.

25. Strem BM & MH Hedrick. The growing importance of fat in regenerative medicine. Trends in Biotechnology 2005: 23(2);64-66

26. Patrick CW. Tissue Engineering Strategies for Adipose Tissue Repair. The Anatomical Record 2001: 263;361-366.

27. Kitagawa Y & N Kawaguchi. De novo adipogenesis for reconstructive surgery. Cytotechnology 1999: 31;29-35.

28. Yoo G & JS Lim. Tissue Engineering of Injectible Soft Tissue Filler: Using Adipose Stem Cells and Micronized Acellular Dermal Matrix. Journal of Korean Medical Science 2009: 24;104-109

29. Cho SW, SS Kim, JW Rhie, HM Cho, CY Choi, & BS Kim. Engineering of volume-stable adipose tissues. Biomaterials 2005: 26;3577-3585.

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